General

Guideline Title

Routine HPV testing in head and neck squamous cell carcinoma.

Bibliographic Source(s)

Lacchetti C, Waldron J, Perez-Ordonez B, Kamel-Reid S, Cripps C, Gilbert R, Head and Neck Cancer DSG. Routine HPV testing in head and neck squamous cell carcinoma. Toronto (ON): Cancer Care Ontario (CCO); 2013 May 13. 58 p. (Evidence-based series; no. 5-9). [103 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Recommendations

Major Recommendations

Recommendation 1

The tumours of all adult patients presenting with oropharyngeal squamous cell carcinomas (SCCs) should be routinely tested for human papillomavirus (HPV) status.

Recommendation 2

It is recommended that the neck nodal tissue of patients with metastatic SCC to neck nodes from an unknown head and neck primary be routinely tested for HPV status.

Recommendation 3

It is recommended that HPV status in oropharyngeal SCC be initially determined using immunohistochemical (IHC) staining for p16.

IHC staining for p16 can be considered positive when the following three criteria are met:

- Cytoplasmic and nuclear staining
- Staining is moderate to strong and diffuse
- Staining is present in at least 50% of tumour cells

Refer to the algorithm on page 5 in the original guideline document for a validated polymerase chain reaction (PCR) or in situ hybridization (ISH) technique for high-risk HPV subtypes that may be necessary to confirm p16 results in selected cases.

Technical Considerations for Recommendation 3

While it is not possible to make evidence-based recommendations regarding the minimum set of criteria requiring adherence in a pathology laboratory with respect to HPV testing at this time, the following guidance is offered based on expert opinion and a consensus process by members of the Head and Neck Disease Site Group (DSG):

- Analysis should be performed on sections from paraffin blocks or unstained slides cut at 4 microns
- In cases of metastatic disease, where a core biopsy may not be a possibility, all efforts should be made to obtain enough tissue with fine needle aspiration (FNA) to prepare cell blocks.

Clinical Algorithm(s)

An algorithm on validated polymerase chain reaction (PCR) or in situ hybridization (ISH) technique for high-risk human papillomavirus (HPV) subtypes is provided in the original guideline document.

Scope

Disease/Condition(s)

Head and neck squamous cell carcinoma

Guideline Category

Diagnosis

Evaluation

Screening

Clinical Specialty

Internal Medicine

Oncology

Otolaryngology

Pathology

Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Health Care Providers

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the appropriateness of, and make recommendations on, routine testing for human papillomavirus (HPV) status in adult patients with primary, or neck nodal metastatic, squamous cell carcinoma (SCC) of the head and neck

Target Population

Adult patients with squamous cell carcinomas (SCCs) arising in oropharynx, larynx, hypopharynx, nasopharynx, sinonasal tract, or oral cavity subsites or an unknown primary head and neck site

Interventions and Practices Considered

1. Testing of oropharyngeal squamous cell carcinoma (SCC) tumours for human papillomavirus (HPV) status
2. Testing of neck nodal tissue of patients with metastatic SCC from an unknown head and neck primary for HPV status
3. Use of immunohistochemical (IHC) staining for p16 to determine HPV status, with confirmation by validated polymerase chain reaction (PCR) or in situ hybridization (ISH) technique for high-risk HPV subtypes in select cases

Major Outcomes Considered

- Overall survival
- Progression-free survival
- Disease-specific survival
- Prevalence of human papillomavirus (HPV)-associated squamous cell carcinoma (SCC)
- Sensitivity, specificity, and concordance/correlation of diagnostic testing methods

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search

The literature was searched using MEDLINE (OVID: 1996 through March Week 4, 2013), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (April 09, 2013), EMBASE (OVID: 1996 through 2013, Week 14), and the Cochrane Library (OVID: 1st Quarter 2013). In addition, the proceedings of the meetings of the American Society of Clinical Oncology (ASCO), the American Society of Therapeutic Radiology and Oncology (ASTRO), and the European Society for Radiotherapy and Oncology (ESTRO) were all searched for relevant abstracts from 2007 to 2010. Reference lists of studies deemed eligible for inclusion were scanned for additional citations.

The literature search of the electronic databases combined disease-specific terms (squamous cell carcinoma, cancer, malignancy, neoplasm,

tumour) along with site-specific terms (oropharynx, larynx, hypopharynx, oral cavity) and testing-specific terms (HPV, p16, immunohistochemistry, polymerase chain reaction, in situ hybridization) for all study designs (see Appendix 1 in the original guideline document). After this initial literature search was completed, the Working Group recognized the need to include an additional question on HPV and cancers of unknown primaries (CUPs). That systematic search was conducted in June 2012 and updated in April 2013 in MEDLINE and EMBASE for all study designs (see Appendix 2 in the original guideline document).

A priori decision rules were established that specified only comprehensive systematic reviews with relevance to at least one of the three original questions posed would receive formal quality assessments. Identified systematic reviews that required further consideration based on the criteria above were assessed using the 'assessment of multiple systematic reviews' (AMSTAR) tool. The results of the AMSTAR assessment were used to determine whether or not an existing review could be incorporated as part of the evidentiary base. Any identified reviews that did not meet the criteria above, whose AMSTAR assessment indicated important deficiencies in quality, or that were otherwise not incorporated as part of the evidence base would be reported in the reference list, but not further described or discussed.

Further to the searches of the electronic databases, an internet search of Canadian and international health organizations and the National Guideline Clearinghouse was conducted for existing guidelines and systematic reviews relevant to the research questions. Guidelines were included if they were published since 2008 in English. This environmental scan yielded one practice guideline. The Working Group decided that proceeding with a new systematic review that includes the latest research was warranted given the lack of reporting of the literature included in this practice guideline.

Study Selection Criteria and Protocol

Inclusion Criteria

Articles were eligible for inclusion in this systematic review of the evidence if they met the following criteria:

Human Papillomavirus (HPV) Positivity

- Full reports or abstracts of phase III randomized controlled trials that evaluated tumour HPV status and clinical outcome
- Studies that included adult patients with squamous cell carcinomas arising in the oropharynx, larynx, hypopharynx, nasopharynx, sinonasal tract, or oral cavity
- Results were reported for one or more of the following outcomes: overall survival, disease-free survival, disease-specific survival or progression-free survival.

Prevalence

- Studies that included a minimum of 50 cases of head and neck squamous cell carcinoma (HNSCC)
- Testing that included a clearly described detection method of interest
- Prevalence of HPV-associated tumours for any of the following subsites is reported: oropharynx, larynx, hypopharynx, nasopharynx, sinonasal tract or oral cavity

Unknown Primaries

- Studies that included a minimum of 20 cases of nodal metastatic squamous cell carcinoma from an unknown head and neck primary
- Testing that included a clearly described detection method of interest
- Results were reported for one or more of the following outcomes: prevalence of HPV-associated metastatic squamous cell carcinoma, correlation between HPV positivity and later detection of the primary tumour, or the sensitivity and specificity of a test for a diagnosis of an oropharyngeal tumour

Testing

- Comparative studies that evaluated the following HPV detection methods: p16 immunohistochemistry (IHC), polymerase chain reaction (PCR), or in situ hybridization (ISH)
- Concordance between detection methods or sensitivity and specificity of the detection method are reported or enough information is provided to allow for the calculation of these outcomes, using PCR for high-risk HPV as the gold standard comparator

Exclusion Criteria

Articles published in languages other than English were excluded because of limited translation resources.

A review of the titles and abstracts that resulted from the search was done by one reviewer. For those items that warranted full-text review, one reviewer reviewed each item with collaboration from a second reviewer if uncertainty existed.

Number of Source Documents

Thirty-six studies met the inclusion criteria and were included in the systematic review.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Assessment of Study Quality and Potential for Bias

All eligible studies underwent data extraction independently by a research methodologist, with all extracted data and information subsequently audited by an independent auditor. The following data were among the items recorded for each study: (a) author and year of publication, (b) patient population, human papillomavirus (HPV) status and sample size, (c) tumour site, and (d) outcomes of interest. Ratios, including hazard ratios (HR), were expressed such that a ratio <1.0 indicates a survival benefit favouring HPV-positive patients; conversely, a survival benefit that favours HPV-negative patients is expressed by a HR >1.0.

An assessment of study quality was performed for all the included evidence by one methodologist. Systematic reviews and meta-analyses were assessed for quality using the 'assessment of multiple systematic reviews' (AMSTAR) tool. For studies that re-analyzed results of completed randomized clinical trials (RCTs), no specific instrument was used, but items such as pre-specified versus post hoc analyses, differences in baseline characteristics between patients whose HPV status was assessed and those in which it was not, and power calculations for subgroups analyses were reported on. Methodological criteria assessed for other study designs were informed by the Newcastle-Ottawa Quality Assessment Scale and included study design, type of data collection, sampling method, and blinding in outcome assessment. Blinding of the quality assessor to the author, institution or journal was not considered necessary.

Synthesizing the Evidence

When clinically homogenous results from two or more trials were available, the data was pooled using the Review Manager software (RevMan 5.1) provided by the Cochrane Collaboration. Since HR, rather than the number of events at a certain time point, are the preferred statistic for pooling time-to-event outcomes, those were extracted directly from the most recently reported trial results. The variances of the hazard ratio estimates were calculated from the reported confidence intervals (CI). A random effects model was used for all pooling.

Statistical heterogeneity was calculated using the χ^2 test for heterogeneity and the I^2 percentage. A probability level for the χ^2 statistic less than or equal to 10% ($p \leq 0.10$) and/or an I^2 greater than 50% were considered indicative of statistical heterogeneity. Results are expressed as hazard ratios with 95% CI.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The Head and Neck Disease Site Group (DSG) asked the Program in Evidence-based Care (PEBC) to develop a guideline on routine testing of human papillomavirus (HPV) in head and neck squamous cell carcinomas (SCC). In consultation with the Head and Neck DSG, a Working Group was identified from the DSG membership. Additionally, two experts in the field of pathology and laboratory medicine were invited to join the working group. This Working Group consisted of one radiation oncologist, one medical oncologist, one head and neck surgeon, one pathologist, one laboratory medicine specialist and one methodologist. The Working Group and DSG also formed the Routine HPV Testing in Head & Neck SCC GDG. This group would take responsibility for providing feedback on the guideline as it was being developed and acted as the Expert Panel for the document at Internal Review, reviewing the document and requiring changes as necessary before approving it.

In order to make recommendations as part of a clinical practice, the Working Group and the Head and Neck Cancer DSG developed the evidentiary base upon which the recommendations are based. Based on the objectives of the guideline, the Working Group derived the research questions outlined below.

Research Questions

1. What is the relationship between HPV positivity and outcome in head and neck squamous cell carcinomas (HNSCC)?
2. In which head and neck subsites is the prevalence of HPV-associated squamous cell carcinoma high enough to justify routine testing of HPV positivity?
3. What is the diagnostic and prognostic value of routine testing of HPV status in patients with neck nodal metastatic squamous cell carcinoma from an unknown head and neck primary?
4. What is the optimal testing method for the identification of HPV positivity in head and neck squamous cell carcinomas?

Methods

The evidentiary base was developed using a planned two-stage method:

1. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews are identified that address the research questions and are of reasonable quality, then those systematic reviews would form the core of the evidentiary base.
2. Systematic review of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

Initial Recommendations

Using the evidentiary base in Section 2 of the original guideline document, the Working Group developed a set of initial recommendations. These initial recommendations were developed through a consideration of the aggregate-evidence quality and the potential for bias in the evidence and the likely benefits and harms of routine HPV testing. The Working Group considered the values they used in weighing benefits compared to harms, and then made a considered judgement. This process is described in detail for each topic area in the original guideline document.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Internal Review

Almost all Program in Evidence-based Care (PEBC) documents undergo internal review. This review is conducted by the Expert Panel and the Report Approval Panel (RAP). The Working Group was responsible for incorporating the feedback and required changes of both of these panels, and both panels had to approve the document before it could be sent to External Review.

Expert Panel Review and Approval

The Head and Neck Disease Site Group (DSG) acted as the Expert Panel for this document. The document must be approved by a formal vote. In order to be approved, 75% of the Head and Neck DSG membership must cast a vote or abstain, and of those that vote, 75% must approve the document. At the time of the voting, the Head and Neck DSG members could suggest changes to the document, and possibly make their approval conditional on those changes. In those cases, the Working Group was responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval.

The Head and Neck DSG reviewed the document during the fall of 2012. During this review, the Head and Neck DSG unanimously approved the document and no changes were requested nor made.

On January 6, 2013, by email, the Head and Neck DSG formally approved the document by vote. Of the 14 members of the Head and Neck DSG (who were not part of the working group), 11 members cast votes, for a total of 79% response. Of those who cast votes, all 11 approved the document (100%).

RAP Review and Approval

The purpose of the RAP review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of nine clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. For each document, three RAP members review the document: the Director and two others. RAP members must not have had any involvement in the development of the guideline prior to Internal Review. All three RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made, with the Assistant Director of Quality and Methods, PEBC, making a final determination that the RAP's concerns have been addressed.

In December 2012, the RAP reviewed and approved this document.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the Head and Neck DSG circulated the draft document with recommendations to external review participants for review and feedback.

Methods

Targeted Peer Review

During the guideline development process, five targeted peer reviewers from Ontario, Canada and across the United States considered to be clinical and/or methodological experts on the topic were identified by the working group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Five reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on February 5, 2013. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Working Group reviewed the results of the survey.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. All clinicians in Ontario in the PEBC database whose discipline was categorized as pathology and laboratory medicine or head and neck were contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (see Section 1 in the original guideline document) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (see Section 1 in the original guideline

document) and the evidentiary base (see Section 2 in the original guideline document). The notification email was sent on February 5, 2013. The consultation period ended on March 19, 2013. The Working Group reviewed the results of the survey. During the professional consultation phase, the PEBC was contacted by the College of American Pathologists (CAP) for an opportunity to also review the draft report. The draft report was provided to four CAP chairs, three of which provided written feedback.

Conclusion

This Evidence-Based Series (EBS) report reflects the integration of feedback obtained through the external review process with final approval given by the Head and Neck DSG and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by randomized and non-randomized trials.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- There is evidence from a meta-analysis of randomized trials that human papillomavirus (HPV)-positivity is a strong predictor of prognosis in patients with oropharyngeal squamous cell carcinoma. In addition, it is likely that HPV status will influence management decisions in the near future and is now regarded as a mandatory stratification factor for clinical trials. Therefore, even though at this time no recommendation can be made to base clinical management decisions on HPV status, the valuable prognostic benefits of HPV testing are sufficient to warrant routine testing.
- The evidence indicates that there is relationship between HPV positivity and whether the initial cancer arises in the oropharynx or not. As detection of the primary tumour offers a reduction in morbidity due to the benefits of localized treatment, the additional diagnostic information provided by HPV status is sufficient to warrant routine testing of these tissues.
- The current evidence suggests that polymerase chain reaction (PCR), deoxyribonucleic acid in situ hybridization (DNA ISH), and immunohistochemical (IHC) staining are all comparable. With no unequivocal evidence exclusively supporting any particular scheme, the Head & Neck Disease Site Group (DSG) believes this scheme is practical and simple, and it minimizes the impact of testing on available pathology resources and is appropriate until such time as further evidence becomes available. The Head & Neck DSG acknowledges that the algorithm in the original guideline document may be considered controversial by some, but it is believed to address the proficiencies that are most readily available in laboratories across the province.

Potential Harms

Not stated

Qualifying Statements

Qualifying Statements

- Recommendation 1 only applies to patients with squamous cell carcinoma of the oropharynx, which includes tonsil, base of tongue, soft palate and associated pharyngeal walls. The data and recommendation do not apply to patients with non-oropharyngeal cancers.
- Altering management decisions based on results from human papillomavirus (HPV) testing is not recommended beyond the context of a clinical trial at this time.
- Currently, there are no standardized protocols or extensive published experience regarding the performance of p16 immunohistochemical

(IHC) or HPV in situ hybridization (ISH) in fine-needle aspiration (FNA) or cytology material from metastatic squamous cell carcinoma to cervical lymph nodes.

- The Head & Neck Disease Site Group (DSG) considers quality assurance and quality control in HPV-status testing to be paramount. As such, all testing should be carried out in licensed and accredited laboratories, and test results should be interpreted by experienced pathologists/scientists. Laboratories need to follow proper quality control and participate in external proficiency testing to ensure test accuracy. Further discussion of specific quality and proficiency parameters necessary for individual laboratories performing HPV-status testing is beyond the scope of this guideline.
- Qualitative HPV polymerase chain reaction (PCR) assay detection alone should be avoided.
- The recommendations presented in this guideline do not apply to samples from dental procedures.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Lacchetti C, Waldron J, Perez-Ordonez B, Kamel-Reid S, Cripps C, Gilbert R, Head and Neck Cancer DSG. Routine HPV testing in head and neck squamous cell carcinoma. Toronto (ON): Cancer Care Ontario (CCO); 2013 May 13. 58 p. (Evidence-based series; no. 5-9). [103 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 May 13

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-Based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Head and Neck Cancer Disease Site Group

Composition of Group That Authored the Guideline

For a current list of past and present members, please see the Cancer Care Ontario Web site .

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, Head and Neck Disease Site Group (DSG) members, and internal and external reviewers were asked to disclose potential conflicts of interest. The authors, members, and reviewers reported that they had no conflicts of interest.

Guideline Status

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Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site .

Availability of Companion Documents

The following is available:

- Program in evidence-based care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2012. 14 p. Electronic copies: Available in Portable Document Format (PDF) from the CCO Web site .

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on October 29, 2013.

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